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TOXICOLOGICAL EVALUATION OF PYRETHROID INSECTICIDE (5-BENZYL-3-FURYL) METHYL-2,2-DIMETHYL-3-(2-METHYLPROPENYL) CYCLOPROPANECARBOXYLATE (RESMETHRIN)

STUDY NO. 51-0830-77

OCTOBER 1975 - JANUARY 1977

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ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MD 21010

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(5-benzyl-3-furyl) methyl-2,2-	impregnated cloth	prenatal toxicity
dimethyl-3-(2-methylpropenyl)	skin irritation	teratogenic
cyclopropanecarboxylate	sensitization	mutagenic

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

A toxicity evaluation of the technical grade synthetic pyrethroid insecticide (5-benzyl-3-furyl) methyl-2,2-dimethyl-3-(2-methylpropenyl) cyclopropanecarboxylate (resmethrin) was conducted by this Agency using rats, rabbits, guinea pigs, and dogs. The data in these studies indicate that there should be no toxic hazard to humans from topical exposure to resmethrin nor should resmethrin impregnated cloth, at a limited use concentration of 0.25 mg/cm^2, and 1 percent resmethrin in pyrax powder cause adverse skin reactions.

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TOXICOLOGICAL EVALUATION OF PYRETHROID INSECTICIDE (5-BENZYL-3-FURYL) METHYL-2,2-DIMETHYL-3-(2-METHYLPROPENYL) CYCLOPROPANECARBOXYLATE (RESMETHRIN).
STUDY NO. 51-0830-77

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ABSTRACT

A toxicity evaluation of the technical grade synthetic pyrethroid insecticide (5-benzyl-3-furyl) methyl-2,2-dimethyl-3-(2-methylpropenyl) cyclopropanecarboxylate (resmethrin) was conducted by this Agency using rats, rabbits, guinea pigs, and dogs. The technical grade compound did not produce skin irritation when applied to the intact and abraded skin of rabbits. The compound did not produce a skin sensitization reaction in guinea pigs nor a photochemical skin irritation reaction in rabbits. Repeated applications to the ears of rabbits failed to manifest an acneform dermatitis reaction. The application of technical grade compound on the skin as well as compound impregnated cotton sateen cloth caused only slight skin irritation in a 24-day wear test in rabbits. Data indicate that the compound is nonteratogenic and nonmutagenic. There is little toxic hazard from ingestion of resmethrin based on feeding studies in which a daily ingestion of 1500 mg/kg was required to produce mortality in rats. Daily intravenous dosages of 25 and 10 mg/kg in dogs for 15 days produced no toxic signs, gross abnormalities, nor compound related changes in selected enzyme systems. The data in these studies indicate that there should be no toxic hazard to humans from topical exposure to resmethrin nor should resmethrin impregnated cloth, at a limited use concentration of 0.25 mg/cm^2, and 1 percent resmethrin in pyrax powder cause adverse skin reactions.

(10) K. Clark / [illegible], Richard A. Angerhofer, Everett A. [illegible]

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STUDY NO. 51-0830-77
OCTOBER 1975 - JANUARY 1977

1. AUTHORITY.

a. Memorandum of Understanding Between the US Department of the Army, Office of The Surgeon General, The US Army Health Services Command, The US Army Environmental Hygiene Agency, the Armed Forces Pest Control Board, and the US Department of Agriculture, effective December 1970 with Amendment No. 1, effective August 1974.

b. Letter, AFPCB, Armed Forces Pest Control Board, 21 October 1975, subject: Request for Toxicological Evaluation.

2. REFERENCES.

a. Report, this Agency, Toxicological Evaluation of Pyrethroid Insecticide (5-Benzyl-3-Furyl) Methyl-2,2-Dimethyl-3-(2-Methylpropenyl) Cyclopropanecarboxylate (SBP-1382[tm])*, Special Study No. 51-127-71/72, December 1970 - February 1972, AD 747345.

b. Report, this Agency, Hazard Evaluation of Aerosol Formulations Containing The Synthetic Pyrethroid Insecticide (5-Benzyl-3-Furyl) Methyl-2,2-Dimethyl-3-(2-Methylpropenyl) Cyclopropanecarboxylate (SBP-1382[tm])*, Special Study No. 51-136-71/74, June 1971 - January 1973, AD 770403.

c. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972.

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* SBP-1382 is a registered trademark of CPC International, Inc., S. B. Penick Company, 100 Church Street, New York, NY 10007. Use of trademarked names does not constitute endorsement of the chemical by the US Army, but is used only to assist in identification of a specific compound or instrument.

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3. PURPOSE. These studies were conducted to acquire information concerning the potential health hazards associated with the use of (5-benzyl-3-furyl) methyl-2,2-dimethyl-3-(2-methylpropenyl) cyclopropanecarboxylate (resmethrin). Previous studies by this Agency had developed information relating to handling resmethrin (ref para 2a) and for its use in proposed aerosol formulations (ref para 2b). The present studies were performed to provide information relating to potential exposure hazards resulting from the proposed use of resmethrin for impregnating stored military garments and fabrics (ref para 1b). The information from those studies would provide a basis for advising the Armed Forces Pest Control Board on the potential hazards associated with this use, in accordance with the provisions of the Memorandum of Understanding (ref para 1a).

4. SUMMARY OF FINDINGS.

a. AI3-27474, SBP-1382, and resmethrin are designations for (5-benzyl-3-furyl) methyl-2,2-dimethyl-3- (2-methylpropenyl) cyclopropanecarboxylate. The technical grade compound, 88 percent pure, is an amorphous, waxy, yellow solid. The lot number of the material used in the tests conducted at this Agency was No. 3521-LOV-4. The compound is soluble in acetone and ethanol and insoluble in water. An infrared spectrum of the sample of resmethrin evaluated by this Agency is found in Appendix A. Definitions of selected terms and abbreviations used in this report are found in Appendix B. Tabulation of toxicity doses by various routes of administration are listed in Appendix C. The formulation for artificial (eccrine) sweat is provided in Appendix D. The skin irritation scoring system is provided in Appendix E. Numerical data presented in the appendices are expressed as the mean plus or minus the standard deviation. Statistical significance in this report has been selected at the 0.01 level of probability.

b. A toxicity evaluation of the technical grade synthetic pyrethroid insecticide, resmethrin, was conducted by this Agency using rats, rabbits, guinea pigs, and dogs. The technical grade compound did not produce skin irritation when applied to the intact or abraded skin of rabbits. Repeated applications of the compound to the ears of rabbits did not induce acneform dermatitis. Resmethrin did not sensitize guinea pig skin to subsequent compound exposure nor rabbit skin to UV radiation. The dermal application of 1 percent technical grade compound in pyrax powder, 10 grams of neat compound, as well as compound-impregnated cotton sateen cloth (0.247 mg/cm^2) caused only slight skin irritation in a 24-day wear test in rabbits. Mutagenicity tests with resmethrin using selected yeast and bacterial cultures demonstrated that this compound was nonmutagenic in this in vitro system. Prenatal toxicity was observed in rats at 1500 mg/kg/day consumed in ground feed; however, maternal toxicity was also observed at this dosage level. This compound was nonteratogenic, even at the 1500 mg/kg/day dosage level. Feeding studies demonstrated that the minimum dietary effect dosage of resmethrin in Long-Evans rats was 240 mg/kg/day based on increases in liver-to-body weight ratios. The feeding studies also demonstrated that

resmethrin was more lethal among male rats than female rats in the Wistar derived Sprague-Dawley as well as Long-Evans strains. The intravenous administration of resmethrin in dogs (25 and 10 mg/kg) for 15 days produced no toxic signs, gross abnormalities, nor compound related changes in selected enzyme systems. The results of tests performed at USAEHA indicate that technical grade resmethrin has low potential toxicity and that there is little hazard to man from accidental ingestion or contact with technical grade compound and compound-impregnated cloth. A detailed tabular presentation of toxicity data follows. *

* The experiments reported herein are conducted according to the "Guide for the Care and Use of Laboratory Animals", prepared by the Committee on Revision of the "Guide for Laboratory Animal Facilities and Care", of the Institute of Laboratory Animal Resources, National Research Council (1972). This study was performed in animal facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SKIN IRRITATION STUDIES		
Rabbits		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.		
0.5 gm technical grade compound applied to each of six rabbits.	Resmethrin produced no irritation of the intact or abraded skin.	USAEHA Category I (ref Appendix F). No restriction for acute application to the human skin.
0.5 gm technical grade compound in 1.5 ml acetone applied to each of six rabbits.	Resmethrin produced no irritation at 24 hours but very slight to well defined erythema and very slight edema in two of six rabbits at 72 hours at the intact skin sites and very slight to well defined erythema in three of six rabbits at 72 hours as well as very slight edema at 72 hours to 7 days in two of six rabbits at the abraded skin sites.	USAEHA Category II (ref Appendix F). Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.
1.5 ml solvent control (acetone) applied to each of six rabbits.	Acetone produced no irritation of the intact or abraded skin.	

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TEST	RESULTS	INTERPRETATION
SENSITIZATION STUDIES		
Guinea Pigs (Male)		
Intradermal injections of 0.1 ml of a 0.1 percent suspension (w/v) of resmethrin or of a 0.1 percent suspension of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of normal saline.		
Ten test guinea pigs received and were challenged with a 0.1 percent suspension of resmethrin.	Challenge dose of resmethrin (last intradermal injection) produced no greater response than did the initial injection.	Test compound did not sensitize guinea pigs and is not expected to cause a sensitization reaction in humans.
Ten positive control guinea pigs received and were challenged with a 0.1 percent suspension of DNCB.	Positive control (DNCB) produced sensitization in 9 of 10 guinea pigs.	
Ten cage control guinea pigs. Five receiving challenge dose of resmethrin at 0.1 percent without prior sensitizing doses. Five receiving challenge dose of DNCB at 0.1 percent without prior sensitizing doses.	Challenge dose of resmethrin and DNCB produced no greater response than did the initial injection.	

* A known skin sensitizer.

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TEST	RESULTS	INTERPRETATION
PHOTOCHEMICAL SKIN IRRITATION STUDIES		
Rabbits		
A single application (0.05 ml) of a 10 percent (w/v) solution of the compound and of a 5 percent (w/v) oil of Bergamot solution (positive control) in 95 percent ethyl alcohol, were applied to the intact skin of six New Zealand White rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm. Application area was checked for irritation at 24, 48, and 72 hours.	Resmethrin did not cause a photochemical irritation reaction under test conditions.	Compound did not cause a photochemical irritation reaction under test conditions and is not expected to cause a photochemical irritation reaction in humans.
Control		
Following UV exposure of the rabbits, 0.05 ml of the test compound, positive control, and diluent were applied to additional skin areas to serve as unirradiated control sites.	Resmethrin diluted in ethanol did not cause a primary irritation response in unirradiated areas.	

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TEST	RESULTS	INTERPRETATION
ACNEFORM DERMATITIS STUDY		
Rabbits - Male		
Repeated daily applications of 0.1 g of the technical grade compound to one ear of each of five New Zealand White rabbits for 30 consecutive days.	Compound did not produce an acneform dermatitis reaction under test conditions.	Compound did not produce acneform dermatitis under test conditions and is not expected to produce this type of dermatitis reaction in man.
Control		
Repeated daily applications of 0.1 ml of Bestoil® to one ear of each of five New Zealand White rabbits for 30 days.	Bestoil, the positive control, produced occlusion of follicular orifices or typical "blackhead" formation associated with acneform dermatitis at 11 days in five out of five rabbits.	

®Bestoil is a registered trademark for a high sulfur content cutting oil marketed by the Oster Manufacturing Company, 1300 E 289th St. Wicklife, OH 44092.

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TEST	RESULTS	INTERPRETATION
PRENATAL TOXICITY STUDY		
Rats (Long-Evans)		
Two groups of 30 pregnant rats were placed on the appropriate dietary level of resmethrin in ground feed from Day 6 through Day 15 of gestation. A control group of 30 rats was maintained on untreated food. The compound was added to feed by dissolving measured amounts in acetone and mixing with preground feed in the proportion of 1 liter of acetone per 2 kilograms of feed. Acetone was removed from the feed by steam evaporation. Treated feeds were stored at 4°C. Compound concentrations in ground feed were verified by gas chromatographic analyses. The day that sperm were found in the vaginal smear was designated day 0 of gestation. Twenty rats from each group were sacrificed on day 20 of gestation by intracardiac injection of sodium pentobarbital. The reproductive tracts were exposed by laparotomy, and the copora lutea, implantation sites, and resorption sites were counted. The fetuses were removed, examined for gross abnormalities, and the sex and weight of each fetus recorded. All grossly abnormal fetuses and 50 percent of the apparently normal fetuses were further studied as Bouin-fixed, freehand sections for soft tissue abnormalities or after alizarin red S staining for skeletal malformations. Ten rats from each group were allowed full term pregnancies. Each neonate was examined for gross abnormalities, the sex was noted, and body weights were determined daily for 21 days after which time they were sacrificed and necropsied for gross pathology. Daily oral dosages were: 0* mg/kg/day resmethrin 188 mg/kg/day resmethrin 1500 mg/kg/day resmethrin	Fetuses from females dosed with resmethrin showed no differences from controls in male/female sex ratios, nor gross abnormalities of fetal skeletons and soft tissues. Females from the 1500 mg/kg/day group had tremors and decreased food and water consumption resulting in lower fetal weights. Fifteen of thirty females from the 1500 mg/kg/day totally resorbed the fetuses and two females from this group died during the test. The fetuses from the 1500 mg/kg/day full term pregnant females had significantly lower body weights at birth than control fetuses, however, these weights were not significantly different at 21 days post partum. No gross abnormalities were observed in these neonates at the time of necropsy. Females from the 188 mg/kg/day group did not exhibit toxic signs nor decreased food and water consumption. Fetal weights from these females were comparable to fetal weights from the control group. The weights of the full term neonates from the 188 mg/kg/day group were also comparable to those from the control group. The fetal resorption rate in this group was 1.3 percent compared to a 2.7 percent rate among the control dams. No gross abnormalities were observed among full term neonates from the 188 mg/kg/day group.	The consumption of resmethrin in ground feed by pregnant female rats was not teratogenic at 1500 and 188 mg/kg/day, however, prenatal and maternal deaths were observed when 1500 mg/kg/day was consumed.

* Acetone solvent control.

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TEST	RESULTS	INTERPRETATION
IN VITRO MUTAGENIC EVALUATION*		
One strain of yeast, Saccharomyces cerevisiae (D^4) and five strains of Salmonella typhimurium (TA-1535, TA-1537, TA-1538, TA-98, TA-100) were used in evaluating mutagenic potential. The compound was tested directly and in the presence of liver microsomal enzyme preparations from rats pretreated with Aroclor® 1254.	Resmethrin was not mutagenic for any of the indicator strains employed in these evaluations either directly or in preparations pretreated with the hepatic enzyme inducer Aroclor.	Compound is considered nonmutagenic under these test conditions.

* Work performed under contract by Litton Bionetics, Kensington, Maryland (LBI Project No. 2575, December 9, 1975)
®Aroclor is a registered trademark of Monsanto Chemical Co., 800 N Lindberg Blvd, St Louis, MO.

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TEST	RESULTS	INTERPRETATION
PROLONGED APPLICATION STUDIES		
24-Day Wear Test - Rabbits		
Compound and control materials applied on the skin twice per week for 3 weeks to shaved male New Zealand White rabbits. Specimens for clinical chemistry studies were collected once a week between applications of test materials. Cotton cloth was treated with resmethrin dissolved in acetone.	Synopsis of data is found in Appendices G and H.	
Exposed		
Cotton cloth treated with resmethrin at 0.247 mg/cm^2 applied to each of 10 rabbits.	No significant changes were noted at the end of the 24-day wear test in rabbit body weights and organ-to-body weight ratios of liver, lung, kidney, testes, and spleen. Average dermal irritation scores for rabbits resulting from various treatments with resmethrin were not significantly higher than the control groups and did not increase during the test.	Cotton cloth impregnated with a concentration limited to 0.25 mg/cm^2 resmethrin should not irritate human skin even during prolonged contact.
Cotton cloth treated with resmethrin at 0.247 mg/cm^2 over 1 milliliter of sweat (ref Appendix D) applied to each of 10 rabbits.		
Cotton cloth over 10 grams of technical grade resmethrin applied to each of 10 rabbits.		
Untreated cotton cloth over 1 gram per kilogram of body weight of 1 percent resmethrin in pyrax powder applied to each of 10 rabbits.		
Controls		
Cotton cloth treated with acetone applied to each of 10 rabbits.		
Cotton cloth treated with acetone over 1 milliliter of sweat applied to each of 10 rabbits.		
Untreated cotton cloth over 1 gram per kilogram of body weight of pyrax powder applied to each of 10 rabbits.		

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TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PROLONGED APPLICATION STUDIES		
24-Day Wear Test - Rabbits (cont)		
The following clinical parameters were measured: SGOT SGPT LDH Alkaline Phosphatase BUN	No significant trends were found different from control clinical chemistry values in any of the compound exposed groups. Synopsis of data is found in Appendix I, Tables 1 through 5.	Compound produced no significant compound related changes in selected enzyme systems. Dermal penetration of resmethrin probably did not occur.
All animals were necropsied after the 24th day of the test. Various tissues and organs from each animal were examined for microscopic lesions.*	There were no compound related lesions in the skin nor in any of the other examined tissues and organs.	

* Examined tissues and organs were skin, brain, eye, stomach, small intestine, large intestine, cecum, lung, heart, thyroid, liver, pancreas, adrenal gland, kidney, testes, urinary bladder, skeletal muscle, bone, bone marrow, and trachea.

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TEST	RESULTS	INTERPRETATION
PROLONGED ADMINISTRATION STUDIES		
14-Day Feeding Study - Rats (Sprague-Dawley)		
Groups of six rats from each sex were placed on each dietary level of resmethrin. The chemical was added to feed by dissolving measured amounts of compound in acetone and mixing with ground feed in the proportion of 1 liter of acetone per 2 kilograms feed. Acetone was removed from the feed by steam evaporation. Treated feeds were stored at 4°C. Compound concentrations in ground feed were verified by gas chromatographic analyses.	Synopsis of data is found in Appendix J, Tables 1 and 2 and Appendix K, Tables 1 and 2.	The minimum dietary effect level was found to be 375 mg/kg/day based on the increase of the average liver organ-to-body weight ratio among female rats. The maximum no effect dietary level was 375 mg/kg/day for male rats only.
All animals were necropsied after being maintained on appropriate diets containing resmethrin, for 14 days. Various tissues and organs from each animal were examined for microscopic lesions.*	Compound related histological changes were not observed in any of the examined tissues and organs.	
Rats were maintained on diets containing the following dosage levels of resmethrin in their feed:		

Projected Dosages mg/kg/day	Actual Dosages mg/kg/day	
	Male	Female
0.0†	0.0†	0.0†
375.0	310.0	323.0
750.0	660.0	630.0
1500.0	1250.0	1230.0
3000.0	1923.0	2670.0
6000.0	5100.0	1680.0

Female Rats

6000 mg/kg/day - Five out of six rats died. The average body weight decreased.

3000 mg/kg/day - The mean terminal body weight was significantly lower than the mean terminal control body weight.

1500 mg/kg/day - Lowest dose at which tremors were observed.

375 mg/kg/day - Lowest dose at which there was a significant increase in the liver organ-to-body weight ratio.

Male Rats

6000 mg/kg/day - Five out of six rats died. The average body weight decreased.

3000 mg/kg/day - Three out of six rats died. The average body weight decreased. Lowest dose at which there was a significant increase in the kidney organ-to-body weight ratio.

1500 mg/kg/day - Lowest dose at which there was a significant increase in the testicular organ-to-body weight ratio. Lowest dose at which tremors were observed.

750 mg/kg/day - Lowest dose at which there was a significant increase in the liver organ-to-body weight ratio.

* Examined tissues and organs were eye, brain, lung, testes, kidney, liver, spleen, heart, stomach, pancreas, large intestine, skeletal muscle, bone, urinary bladder, small intestine, ovaries, uterus, and oviduct.

† Acetone solvent control

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PROLONGED ADMINISTRATION STUDIES		
14-Day Feeding Study - Rats (Long-Evans)		
Groups of six rats from each sex were placed on each dietary level of resmethrin. The chemical was added to feed by dissolving measured amounts of compound in acetone and mixing with ground feed in the proportion of 1 liter of acetone per 2 kilograms feed. Acetone was removed from the feed by steam evaporation. Treated feeds were stored at 4°C. Compound concentrations in ground feed were verified by gas chromatographic analyses. All animals were necropsied after being maintained on appropriate diets for 14 days. Various tissues and organs from each animal were examined for microscopic lesions.* Rats were maintained on diets containing the following dosage levels of resmethrin in their feed:	Synopsis of data is found in Appendix L, Tables 1 and 2 and Appendix M, Tables 1 and 2. Compound related histological changes were not observed in any of the examined tissues and organs. Female Rats 3000 mg/kg/day - Six out of six rats died. 1500 mg/kg/day - One out of six rats died. The mean terminal body weight was significantly lower than the mean terminal control body weight. 750 mg/kg/day - Lowest dose at which there was a significant increase in the liver organ-to-body weight ratio. 375 mg/kg/day - Lowest dose at which tremors were observed. Male Rats 3000 mg/kg/day - Six out of six rats died. 1500 mg/kg/day - Three out of six rats died. 750 mg/kg/day - Lowest dose at which tremors were observed. 375 mg/kg/day - Lowest dose at which there was a significant increase in the liver organ-to-body weight ratio.	The minimum dietary effect level was found to be 375.0 mg/kg/day based on the increase of the average liver organ-to-body weight ratio among male rats. The maximum no effect dietary level was 188 mg/kg/day for both female and male rats.

Projected Dosages mg/kg/day	Actual Dosages mg/kg/day	
	male	female
0.0†	0.0†	0.0†
94.0	60.9	90.0
188.0	147.9	180.0
375.0	297.3	386.0
750.0	584.0	668.0
1500.0	1375.0	1040.0
3000.0	1266.0	2532.0

* Examined tissues and organs were eye, brain, lung, testes, kidney, liver, spleen, heart, stomach, pancreas, large intestine, skeletal muscle, bone, urinary bladder, small intestine, ovaries, uterus, and oviduct.
† Acetone solvent control.

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TEST	RESULTS	INTERPRETATION
PROLONGED ADMINISTRATION STUDIES		
90-Day Feeding Study - Long Evans Rats		
Groups of 10 male and 10 female rats each were placed on the appropriate dietary level of resmethrin. The chemical was added to feed by dissolving measured amounts of compound in acetone and mixing with preground feed in the proportion of 1 liter of acetone per 2 kilograms of feed. Acetone was removed from the feed by steam evaporation. Treated feeds were stored at 4° C. Compound concentrations in ground feed were verified by gas chromatographic analyses. A general description of the test plan is found in Appendix N.	Synopsis of data is found in Appendix O, Tables 1 and 2 and Appendix P, Tables 1 and 2.	The minimum dietary effect level was found to be 240.0 mg/kg/day based on the increase of the average liver organ-to-body weight ratio among female and male rats. The maximum no effect dietary level was 75 mg/kg/day for both female and male rats.
Rats were maintained on diets containing the following dosage levels of resmethrin in their feed:	**Female Rats**	
Males / **Females** 10 — 0.0 mg/kg/day acetone solvent control — 20 0 — 3.0 mg/kg/day — 10 0 — 8.0 mg/kg/day — 10 10 — 25.0 mg/kg/day — 10 10 — 75.0 mg/kg/day — 10 10 — 240.0 mg/kg/day — 10 8 — 750.0 mg/kg/day — 10 0 — 2400.0 mg/kg/day — 10	2400 mg/kg/day - Ten out of ten rats died. 750 mg/kg/day - The mean terminal body weight was significantly lower than the mean terminal control body weight. Lowest dose at which tremors were observed. 240 mg/kg/day - Lowest dose at which there was a significant increase in the liver organ-to-body weight ratio.	

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TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PROLONGED ADMINISTRATION STUDIES (cont)		
90-Day Feeding Study - Long Evans Rats (cont)	Male Rats	
	750 mg/kg/day - The mean terminal body weight was significantly lower than the mean terminal control body weight. Lowest dose at which there were significant increases in the heart and testicular organ-to-body weight ratios. Tremors were observed.	
	240 mg/kg/day - Lowest dose at which there were significant increases in the liver and kidney organ-to-body weight ratios.	
The following clinical parameters were measured in serum from blood samples taken immediately before necropsy: SGOT SGPT LDH Alkaline Phosphatase Gamma Glutamyl Transpeptidase Bilirubin Total Protein BUN	No significant trends were found different from control clinical chemistry values in test rats which ingested resmethrin for 90 days. Synopsis of data is found in Appendix Q, Tables 1 and 2.	Compound produced no significant compound related changes in selected enzyme systems.
All animals were necropsied after being maintained on appropriate diets for 90 days. Various tissues and organs were examined for microscopic lesions.*	Compound related histological changes were not observed in any of the examined tissues and organs.	

* Examined tissues and organs were eye, brain, lung, testes, kidney, liver, spleen, heart, stomach, pancreas, large intestine, skeletal muscle, bone, urinary bladder, small intestine, ovaries, uterus, and oviduct.

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TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PROLONGED ADMINISTRATION STUDIES		
Dogs (male)		
Intravenous injections of 25 mg/kg of resmethrin in 95 percent ethyl alcohol (250 mg/ml) 5 days a week for 3 weeks in three male Beagle dogs. Blood samples were drawn twice weekly for blood clinical chemistry studies.	All animals appeared grossly normal and no signs were noted after 21 test days.	
Intravenous injections of 10 mg/kg of resmethrin in 95 percent ethyl alcohol (100 mg/ml) 5 days a week for 3 weeks in three male Beagle dogs. Blood samples were drawn twice weekly for blood clinical chemistry studies.	There were no significant differences in organ-to-body weight ratios between test and control animals. Synopsis of data is found in Appendix R.	
Intravenous injections of 0.1 ml/kg of 95 percent ethyl alcohol (solvent control) 5 days a week for 3 weeks in five male Beagle dogs. Blood samples were drawn twice weekly for blood clinical chemistry studies.		
All animals were necropsied at the end of the 21-day test period. Various tissues and organs were examined for microscopic lesions.*		
The following clinical parameters were measured: SGOT SGPT LDH Alkaline Phosphatase Bilirubin Gamma Glutamyl Transpeptidase BUN Sodium Potassium RBC Cholinesterase Plasma Cholinesterase	Compound related histological changes were not observed in any of the examined tissues and organs. The only unequivocal compound related changes were the injection cellulitis, associated vasculitis, and the drainage of blood from those lesions into regional lymph nodes due to repeated compound injections. No significant trends were found different from control clinical chemistry values in any test dog given 10 mg/kg or 25 mg/kg resmethrin per day for 18 days. Synopsis of data is found in Appendix S, Tables 1 through 4.	Compound produced no significant compound related changes in selected enzyme systems.

* Examined tissues and organs were spinal chord, eye, brain, lung, trachea, heart, tonsil, lymph node, esophagus, stomach, small intestine, cecum, bone marrow, large intestine, pancreas, liver, adrenal gland, kidney, spleen, urinary bladder, prostate, tongue, skin, skeletal muscle, thyroid gland, parathyroid gland, salivary gland, bone, and testes.

5. DISCUSSION.

a. The results of toxicity studies performed by USAEHA show that large doses of resmethrin are necessary to cause toxic responses in animals. The findings indicate that resmethrin should not present any significant potential health hazard to man as a consequence of accidental or unavoidable contact with the technical grade compound.

b. A single application of technical grade compound did not irritate rabbit skin in this study, but application of a 33 percent (w/v) solution in acetone produced mild primary irritation of intact skin and skin surrounding abraded areas. Little irritation would be expected from a single topical application of technical grade compound since there was only a slight difference between the gross skin irritation scores of exposed and control rabbits during the 24-day wear test in which rabbit skin was exposed to repeated applications of resmethrin-impregnated cloth (0.247 mg/cm^2), technical grade resmethrin (10 g), and 1 percent resmethrin in pyrax powder.

c. Animal data from skin sensitization studies indicate that resmethrin would not be expected to sensitize human skin to subsequent compound exposure nor cause a photochemical irritation reaction from exposure to sunlight.

d. Prenatal toxicity in rats which consumed resmethrin in ground feed, was observed only at a dosage (1500 mg/kg/day) high enough to kill adult rats.

e. These studies show that resmethrin is nonteratogenic in rats and nonmutagenic in an in vitro test system and indicate that it would probably not be detrimental to man.

f. A dosage level of 1500 mg/kg/day was necessary to produce mortality in rats which ingested the compound in ground feed in 14 and 90 day feeding studies even though toxic signs such as tremors were observed at the 375 mg/kg/day dosage level.

6. CONCLUSIONS. Technical grade resmethrin does not present any acute toxic hazard to man from accidental ingestion or topical exposure. A concentration not exceeding 0.25 mg/cm^2 of the synthetic pyrethroid insecticide resmethrin as a clothing impregnant or 1 percent resmethrin in pyrax powder should present no toxic hazard to man.

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b. A single application of technical grade compound did not irritate rabbit skin in this study, but application of a 33 percent (w/v) solution in acetone produced mild primary irritation of intact skin and skin surrounding abraded areas. Little irritation would be expected from a single topical application of technical grade compound since there was only a slight difference between the gross skin irritation scores of exposed and control rabbits during the 24-day wear test in which rabbit skin was exposed to repeated applications of resmethrin-impregnated cloth (0.247 mg/cm^2), technical grade resmethrin (10 g), and 1 percent resmethrin in pyrax powder.

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7. RECOMMENDATIONS. Approval should be given for the use of the synthetic pyrethroid insecticide (5-benzyl-3-furyl) methyl-2,2-dimethyl-3-(2-methylpropenyl) cyclopropanecarboxylate (resmethrin) as a clothing impregnant or as a 1 percent dust in pyrax powder (auth para 1b). The use concentration should not exceed 0.25 mg/cm^2 in cloth or 1 percent dust in pyrax powder.

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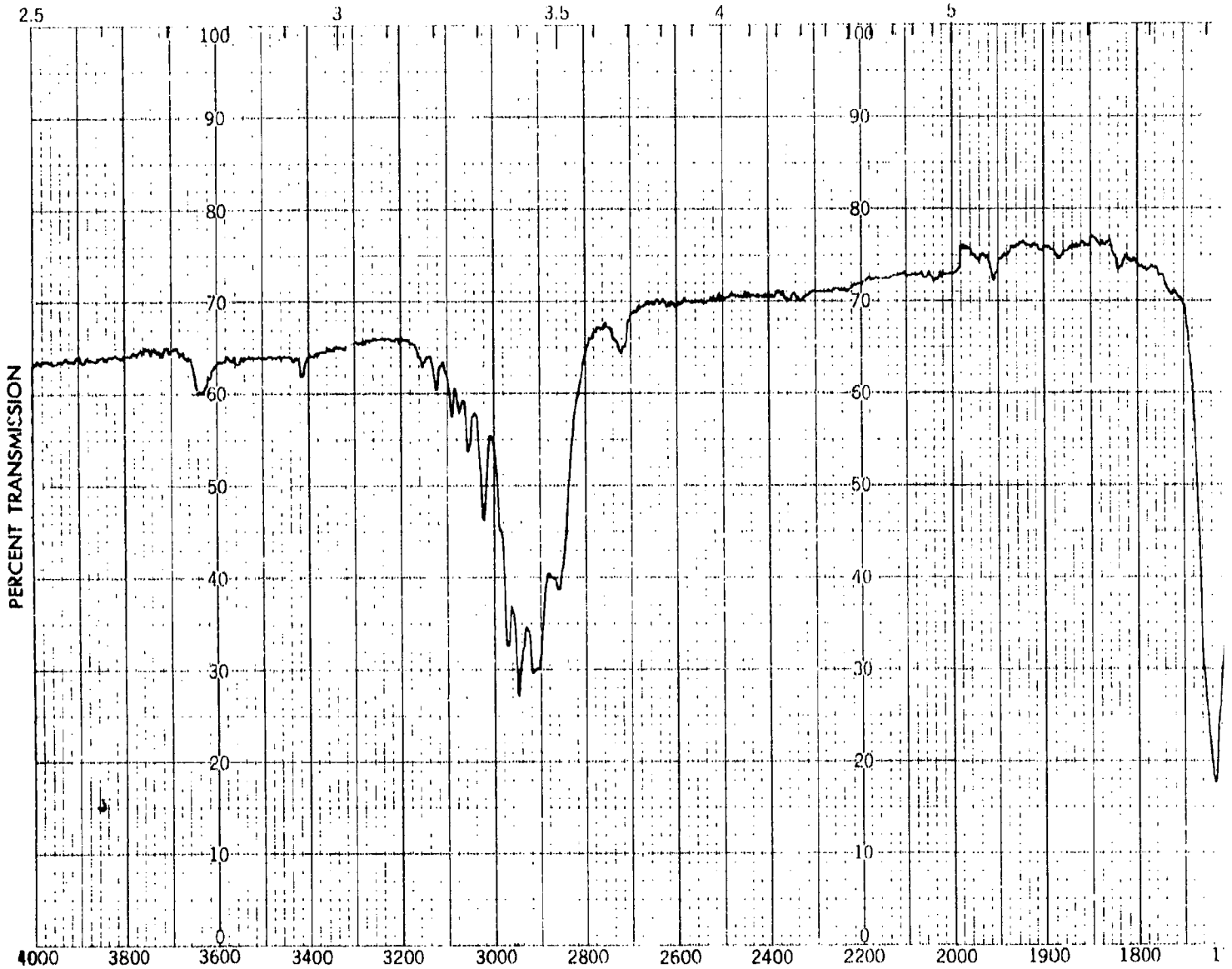
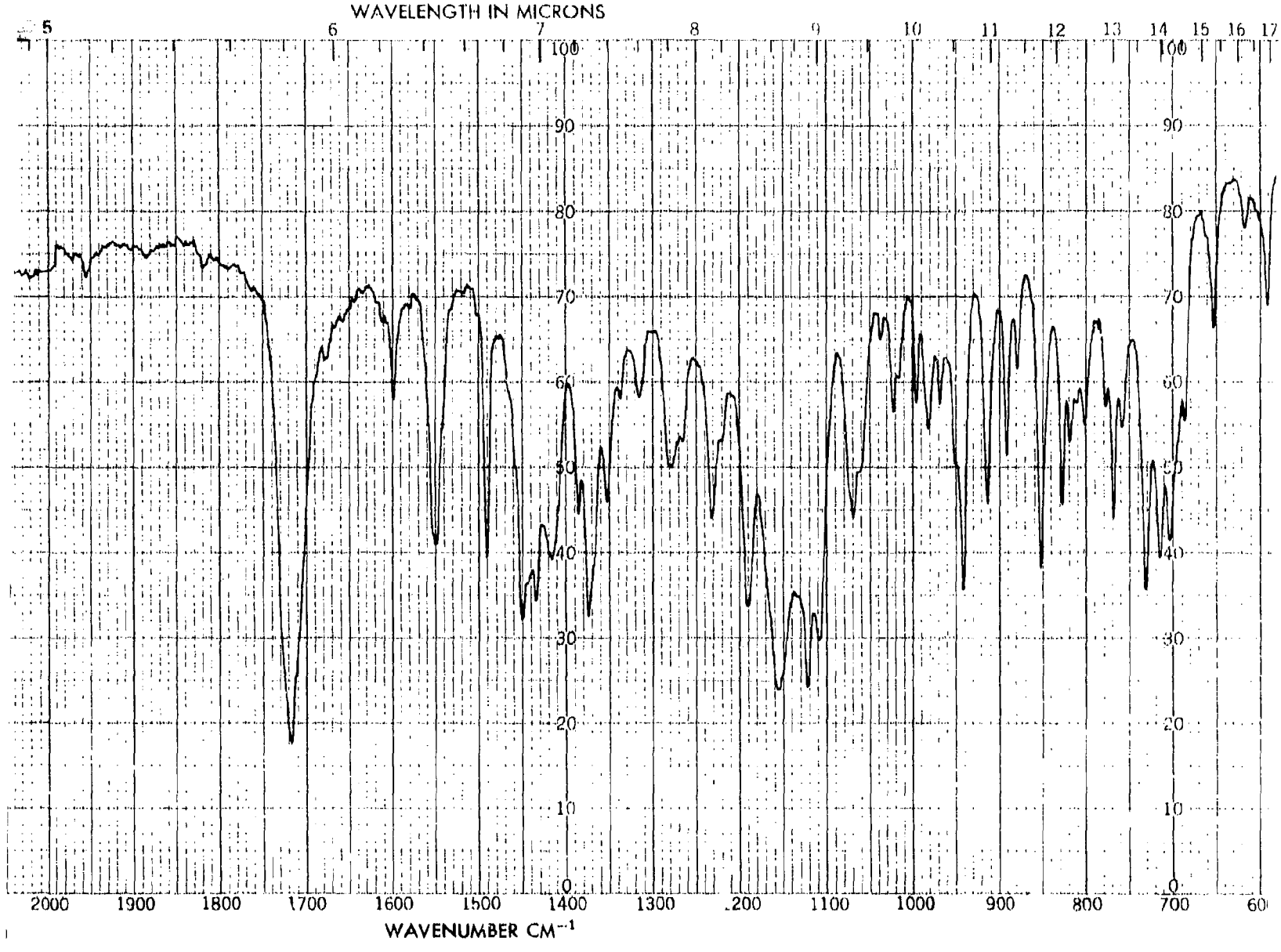


SAMPLE: (5-BENZYL-3-FURY
(2-METHYLPROPEN
(RESMETHRIN)

SLIT: ROUTINE

SPEED: 200 CM^{-1}/MIN

APPENDIX A



LE: (5-BENZYL-3-FURYL) METHYL-2,2-DIMETHYL-3-(2-METHYLPROPENYL) CYCLOPROPANECARBOXYLATE (RESMETHRIN)

GAIN: 3%

ROUTINE

PERIOD: 2

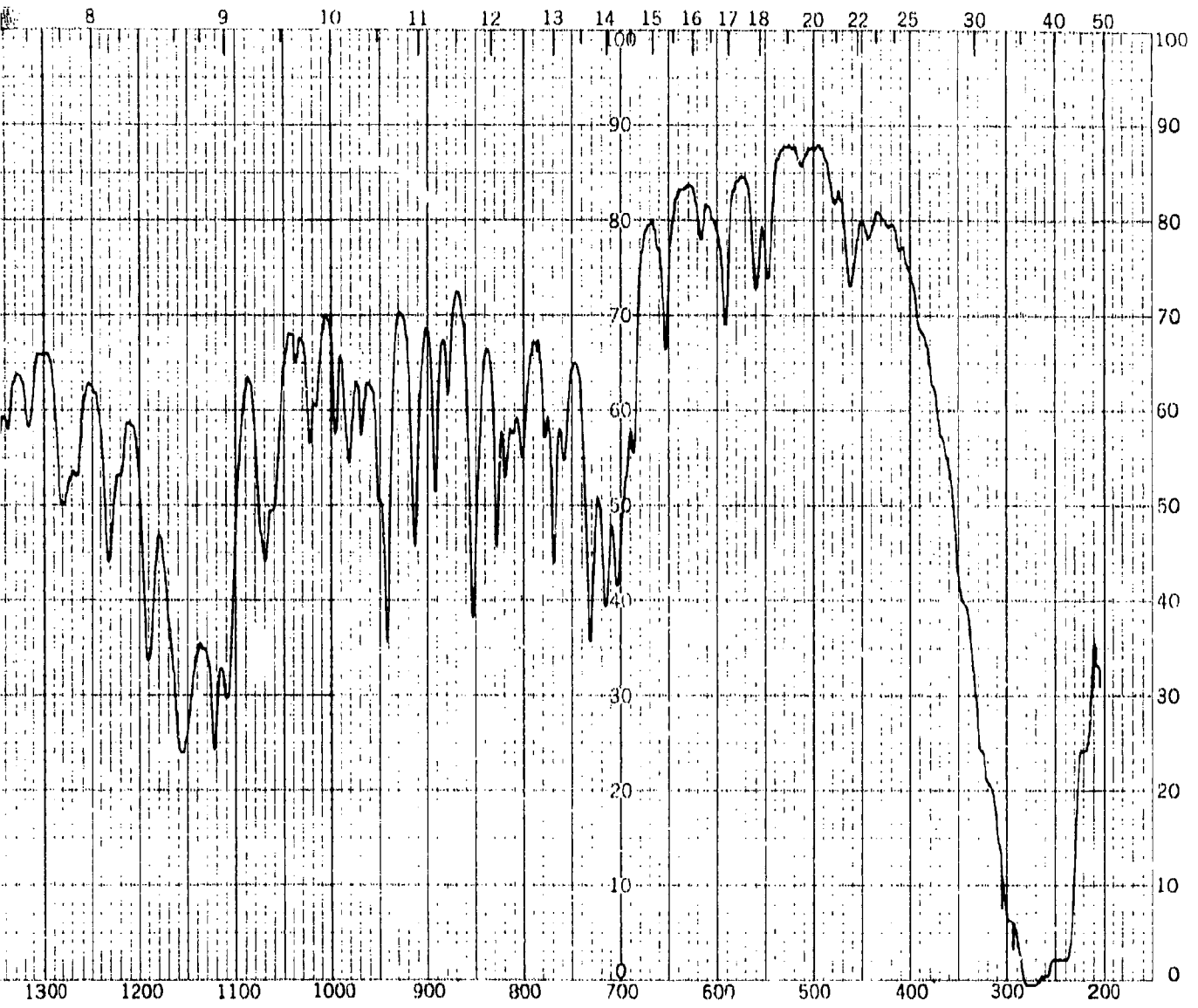
D: 200 CM^{-1}/MIN

ORDINATE: 0-100%T

2

A^{-1}

INFRARED SPECTRUM



GAIN: 3%

YLATE

PERIOD: 2

ORDINATE: 0-100%T

3

APPENDIX B

GLOSSARY OF RECURRING DEFINITIONS, ABBREVIATIONS AND SYMBOLS USED BY THE TOXICOLOGY DIVISION, USAEHA

Definitions of medical terms and abbreviations used in this report are in agreement with the New Gould Medical Dictionary, Second Edition, published by the Blakiston Division of McGraw-Hill Book Company, Inc. Statistical terms and abbreviations are in agreement with those found in J. Maxwell Little's, An Introduction to the Experimental Method, 1961, Burgess Publishing Company, Minneapolis, Minn. The following terms and abbreviations are either not found in the above references or have been modified to fit the special purposes of this report. Some of the terms have been included below for special emphasis.

DEFINITIONS

WORD	DEFINITION
Acute Exposure or Application	One exposure to exogenous test material for no longer than 8 hours. Animals are normally observed for 14 days after exposure.
Approximate Lethal Dose	In range finding the first dose of the lowest series of three ascending doses (each being 50 percent higher in concentration than the previous) all of which produce fatalities.
Chronic Exposure	Repeated daily or constant exposure to a test material for 180 or more days. Postexposure observation period will vary.
Garry and Routh Unit	That amount of cholinesterase activity which causes the liberation of one micromole of SH groups from acetylthiocholine in 3 minutes at 37°C per milliliter of serum, plasma, or packed red cells or per gram tissue.
Hazard Evaluation	A study performed to estimate the degree of danger associated with the use of a material under specified conditions of use.
International Unit/Liter	That amount of enzyme which will catalyze the transformation of 1μmole of the substrate per minute under defined conditions. Analyses in these studies were performed at 37°C.

mg/dl	Milligrams per deciliter
Primary Irritation	A local inflammatory reaction of the skin, produced by a compound, which does not produce destruction or irreversible change at the site of contact.
Skin Sensitizer	A compound which produces an allergic dermatitis under the conditions of the test.
Subchronic Exposure	Repeated daily or constant exposure to a test material for no longer than 179 days or less than 2 days. Post observation period will vary.
Technical Grade Compound	As produced by the manufacturers for their commercial compound; definition dependent upon manufacturer's criteria.

ABBREVIATIONS

ABBREVIATION	MEANING
ALD	approximate lethal dose
BUN	blood urea nitrogen
DNCB	dinitrochlorobenzene
ED	effective dose
GGTP	Gamma Glutamyl Transpeptidase
Hb	hemoglobin
ip	intraperitoneal
IR	infrared
iv	intravenous
LC_{50} (96 hours)	the concentration of a liquid required to kill 50 percent of those exposed for 96 hours.
LDH	lactic dehydrogenase
LD_{50}	median lethal dose
$p = < 0.01$	The probability of the change from normal or control being due to chance alone is less than 1 out of 100.
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
sc	subcutaneous
SD	standard deviation
SE	standard error

APPENDIX C

TABULATION OF TOXICITY DOSES*

VARIOUS ROUTES OF ADMINISTRATION

Commonly Used Terms	LD_{50} Single Oral Dose Rats	Inhalation 4-Hr Vapor Exposure Mortality 2/6 - 4/6 Rats	LD_{50} Skin Rabbits
Highly toxic	50 mg/kg or less	100 ppm or less	43 mg/kg or less
Toxic	51-500 mg/kg	101-1,000 ppm	44-350 mg/kg
Moderatly toxic	501-5,000 mg/kg	1,001-10,000 ppm	351-2,800 mg/kg
Slightly toxic	5,001-15,000 mg/kg	10,001-100,000 ppm	2,801-22,600 mg/kg
Practically nontoxic	above 15,000 mg/kg	>100,000 ppm	above 22,600 mg/kg

* Adapted from Hodge, H. C. and Sterner, J. H. American Industrial Hygiene Association Quarterly, 10:4.93 (December 1943)

APPENDIX D

FORMULATION OF ARTIFICIAL (ECCRINE) SWEAT*

Urea	1.72 gm/l
Glycine	0.20 gm/l
Glucose	0.03 gm/l
Lactic acid	2.50 gm/l
NaCl	1.75 gm/l
KCl	0.22 gm/l
NH_4OH	Sufficient to adjust to pH 5.0

* This formulation includes all constituents described by S. Rothman, "Physiology and Biochemistry of Skin," University of Chicago Press (1954)

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APPENDIX E

EVALUATION OF SKIN REACTIONS*

Erythema and Eschar Formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate-to-severe erythema	3
Severe erythema (beet redness to slight eschar formation)	4

Edema Formation

No edema	0
Very slight (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (edges raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

* An individual irritation score is equal to the sum of the scores for edema formation and erythema and eschar formation.

APPENDIX F

PRIMARY IRRITATION EVALUATION PROGRAM DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING CONSIDERED FOR ACUTE APPLICATIONS

CATEGORY I - (Formerly Categories I and II) - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surround an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

Except when specifically requested for individual compounds, the following Eye Injury Categories A through F, are determined only for those compounds which are in Category I.

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

CATEGORY II - (Formerly Category III) - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant. However, if the compound might come in contact with abraded skin, a prophetic patch test should be conducted on human skin to determine primary irritation potential).

CATEGORY III - (Formerly Category IV) - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals, prior to human testing).

CATEGORY IV - (Formerly Categories V and VI) - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals).

CATEGORY V - (Formerly Category VII) - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans).

APPENDIX G

24-DAY RABBIT WEAR TEST
SUMMARY OF SKIN IRRITATION SCORES* (DORSAL/VENTRAL) MEAN±SD

Type of Application	Day of Test 3	6	10	13	17	20	24
Exposed							
Cotton cloth treated with resmethrin (0.247 mg/cm^2)	0.7 ±0.3	0.7 ±0.3	1.2 ±1.2	0.7 ±0.5	0.6 ±0.5	0.6 ±0.5	0.4 ±0.5
	1.2 ±1.1	0.6 ±0.6	0.6 ±0.7	0.4 ±0.4	0.4 ±0.5	0.4 ±0.6	0.4 ±0.4
Cotton cloth treated with resmethrin (0.247 mg/cm^2) over 1 milliliter of sweat (ref Appendix D)	1.0 ±0.6	0.6 ±0.4	0.5 ±0.5	0.6 ±0.4	0.5 ±0.5	0.5 ±0.3	0.2 ±0.3
	0.5 ±0.8	0.4 ±0.5	0.5 ±0.7	0.2 ±0.3	0.2 ±0.3	0.5 ±0.5	0.4 ±0.4
Cotton cloth treated with acetone over 10 grams of technical grade resmethrin	1.1 ±0.8	1.1 ±0.4	1.6 ±1.2	1.3 ±0.6	0.7 ±0.4	1.1 ±0.7	0.9 ±0.6
	0.9 ±0.9	0.6 ±0.6	0.9 ±0.8	0.9 ±0.7	0.7 ±0.9	0.7 ±0.1	0.7 ±0.6
Untreated cotton cloth over 1 gram per kilogram of body weight of 1 percent resmethrin in pyrax powder	0.8 ±0.6	0.4 ±0.5	0.8 ±0.7	0.2 ±0.3	0.4 ±0.4	0.2 ±0.4	0.2 ±0.4
	0.5 ±0.4	0.5 ±0.6	0.7 ±0.5	0.4 ±0.7	0.5 ±0.6	0.4 ±0.7	0.3 ±0.4
Controls							
Cotton cloth treated with acetone	0.3 ±0.4	0.5 ±0.4	0.5 ±0.5	0.8 ±0.9	0.4 ±0.4	0.4 ±0.4	0.5 ±0.4
	0.5 ±0.8	0.5 ±0.4	0.3 ±0.4	0.3 ±0.4	0.3 ±0.4	0.4 ±0.6	0.3 ±0.4
Cotton cloth treated with acetone over 1 milliliter of sweat	0.6 ±0.5	0.2 ±0.3	0.3 ±0.4	0.6 ±0.6	0.4 ±0.3	0.4 ±0.4	0.2 ±0.3
	0.5 ±0.7	0.3 ±0.4	0.3 ±0.4	0.2 ±0.3	0.2 ±0.3	0.1 ±0.2	0.1 ±0.2
Untreated cotton cloth over 1 gram per kilogram of body weight of pyrax powder	0.8 ±0.4	0.5 ±0.5	0.6 ±0.6	0.5 ±0.4	0.3 ±0.4	0.4 ±0.3	0.3 ±0.1
	1.0 ±0.6	0.6 ±0.6	0.7 ±1.0	0.3 ±0.6	0.5 ±0.4	0.3 ±0.4	0.3 ±0.3

* The irritation scoring system found in Appendix E was used in the evaluation of skin responses.

APPENDIX H

24-DAY RABBIT WEAR TEST
SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS
MALE RABBITS

Type Application	Terminal Body Weight (kg)	Mean Organ-to-Body Weight Ratios (gms/100 gms body weight)±SD Liver	Lung	Kidney	Testes	Spleen
Exposed						
Cotton cloth treated with resmethrin (0.247 mg/cm^2)	3.62 ±0.40	3.25 ±0.64	0.56 ±0.19	0.66 ±0.07	0.16 ±0.04	0.05 ±0.02
Cotton cloth treated with resmethrin (0.247 mg/cm^2) over 1 milliliter of sweat (ref Appendix D)	3.50 ±0.20	3.17 ±0.40	0.68 ±0.18	0.68 ±0.06	0.16 ±0.03	0.05 ±0.02
Cotton cloth treated with acetone over 10 grams of technical grade resmethrin	3.54 ±0.25	3.10 ±0.40	0.84 ±0.20	0.69 ±0.06	0.18 ±0.02	0.04 ±0.01
Untreated cotton cloth over 1 gram per kilogram of body weight of 1 percent resmethrin in pyrax powder	3.45 ±0.40	3.02 ±0.70	0.54 ±0.20	0.66 ±0.10	0.16 ±0.03	0.05 ±0.02
Controls						
Cotton cloth treated with acetone	3.72 ±0.18	3.08 ±0.30	0.65 ±0.20	0.58 ±0.05	0.14 ±0.03	0.03 ±0.01
Cotton cloth treated with acetone over 1 milliliter of sweat	3.77 ±0.32	3.23 ±0.40	0.75 ±0.20	0.65 ±0.06	0.16 ±0.04	0.03 ±0.01
Untreated cotton cloth over 1 gram per kilogram of body weight of pyrax powder	3.55 ±0.47	2.94 ±0.30	0.51 ±0.14	0.68 ±0.10	0.15 ±0.04	0.05 ±0.03

APPENDIX I

TABLE 1. 24-DAY RABBIT WEAR TEST - SUMMARY OF SGOT RESULTS (INTERNATIONAL UNITS/LITER)

Type Application	Pretest (7 weeks) Mean±SD	Period of Test - Mean±SD Day 5	Day 12	Day 19	Day 24
Exposed					
Cotton cloth treated with resmethrin (0.247 mg/cm^2)	18.3 ±4.5	21.5 ±8.7	20.2 ±8.5	25.9 ±16.6	24.9 ±21.9
Cotton cloth treated with resmethrin (0.247 mg/cm^2) over 1 milliliter of sweat sweat (ref Appendix D)	22.6 ±4.9	25.5 ±12.4	17.8 ±5.6	21.7 ±7.5	22.4 ±14.4
Cotton cloth treated with acetone over 10 grams of technical grade resmethrin	16.2 ±4.9	18.0 ±5.8	13.3 ±3.2	16.5 ±3.8	17.6 ±8.8
Untreated cotton cloth over 1 gram per kilogram of body weight of 1 percent resmethrin in pyrax powder	23.4 ±6.8	23.6 ±9.4	23.9 ±11.4	25.4 ±10.8	21.2 ±12.5
Control					
Cotton cloth treated with acetone	19.9 ±4.3	21.9 ±6.5	16.0 ±6.5	18.8 ±7.5	16.5 ±5.2
Cotton cloth treated with acetone over 1 milliliter of sweat	19.1 ±3.5	16.5 ±4.6	14.5 ±4.6	13.6 ±3.1	20.7 ±13.9
Untreated cotton cloth over 1 gram per kilogram of body weight of pyrax powder	18.5 ±3.1	19.0 ±4.2	18.8 ±8.5	28.0* ±12.0	22.3 ±6.3

* Significantly different from pretest mean at 0.01 level of probability.

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TABLE 2. 24-DAY RABBIT WEAR TEST - SUMMARY OF SGPT RESULTS (INTERNATIONAL UNITS/LITER)

Type Application st*	Pretest (7 weeks) Mean±SD	Period of Test - Mean±SD Day 5	Day 12	Day 19	Day 24
Exposed					
Cotton cloth treated with resmethrin (0.247 mg/cm^2)	43.4 ±11.4	52.4 ±14.2	43.1 ±10.9	40.7 ±11.9	41.2 ±10.6
Cotton cloth treated with resmethrin (0.247 mg/cm^2) over 1 milliliter of sweat (ref Appendix D)	38.3 ±11.4	40.5 ±7.5	30.3 ±6.1	31.1 ±7.1	33.1 ±8.4
Cotton cloth treated with acetone over 10 grams of technical grade resmethrin	36.0 ±13.3	53.8* ±25.3	35.2 ±10.2	27.9 ±9.7	28.6 ±10.7
Untreated cotton cloth over 1 gram per kilogram of body weight of 1 percent resmethrin in pyrax powder	51.2 ±16.2	59.5 ±8.3	46.6 ±14.9	42.9 ±9.6	39.7 ±9.3
Controls					
Cotton cloth treated with acetone	33.8 ±12.3	42.9 ±17.4	33.3 ±11.5	25.4 ±10.6	30.2 ±12.5
Cotton cloth treated with acetone over 1 milliliter of sweat	30.7 ±12.3	29.3 ±13.2	29.5 ±8.5	24.1 ±9.0	29.1 ±13.1
Untreated cotton cloth over 1 gram per kilogram of body weight of pyrax powder	42.3 ±12.7	48.6 ±12.2	43.3 ±16.3	38.3 ±13.6	39.7 ±13.1

* Significantly different from pretest mean at 0.01 level of probability.

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TABLE 3. 24-DAY RABBIT WEAR TEST - SUMMARY OF LDH RESULTS (INTERNATIONAL UNITS/LITER)

Type Application	Pretest (7 Weeks) Mean±SD	Period of Test - Mean±SD Day 5	Day 12	Day 19	Day 24
Exposed					
Cotton cloth treated with resmethrin (0.247 mg/cm^2)	159.3 ±54.6	187.8 ±85.4	135.3 ±65.0	194.6 ±54.9	136.7 ±57.7
Cotton cloth treated with resmethrin (0.247 mg/cm^2) over 1 milliliter of sweat (ref Appendix D)	193.5 ±48.2	181.8 ±42.7	147.3 ±58.7	198.3 ±48.2	132.3 ±59.2
Cotton cloth treated with acetone over 10 grams of technical grade resmethrin	119.1 ±37.5	124.6 ±71.7	151.9 ±66.2	90.3 ±32.5	105.1 ±41.3
Untreated cotton cloth over 1 gram per kilogram of body weight of 1 percent resmethrin in pyrax powder	134.9 ±26.1	130.0 ±68.0	155.4 ±85.3	103.1 ±35.0	108.8 ±46.6
Controls					
Cotton cloth treated with acetone	231.8 ±67.2	200.4 ±67.7	119.1 ±73.4	181.4 ±52.7	139.0 ±41.5
Cotton cloth treated with acetone over 1 milliliter of sweat	187.9 ±64.4	199.3 ±63.2	115.9 ±37.5	149.4 ±103.0	214.8 ±57.5
Untreated cotton cloth over 1 gram per kilogram of body weight of pyrax powder	155.6 ±43.8	205.9 ±59.0	148.8 ±68.1	160.0 ±68.4	173.7 ±43.9

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TABLE 4. 24-DAY RABBIT WEAR TEST - SUMMARY OF ALKALINE PHOSPHATASE RESULTS (INTERNATIONAL UNITS/LITER)

Type Application	Pretest (7 Weeks) Mean±SD	Period of Test - Mean±SD Day 5	Day 12	Day 19	Day 24
Exposed					
Cotton cloth treated with resmethrin (0.247 mg/cm^2)	128.0 ±39.4	67.3* ±45.1	67.9* ±34.3	66.2* ±40.7	66.8* ±41.6
Cotton cloth treated with resmethrin (0.247 mg/cm^2) over 1 milliliter of sweat (ref Appendix D)	145.1 ±53.8	70.2* ±21.0	65.2* ±25.4	76.7* ±28.7	68.3* ±20.9
Cotton cloth treated with acetone over 10 grams of technical grade resmethrin	159.3 ±57.5	62.6* ±18.8	57.9* ±16.4	64.3* ±15.9	62.8* ±19.3
Untreated cotton cloth over 1 gram per kilogram of body weight of 1 percent resmethrin in pyrax powder	145.3 ±44.3	68.0* ±30.6	69.7* ±28.3	72.2* ±29.6	63.1* ±25.1
Controls					
Cotton cloth treated with acetone	133.2 ±39.2	66.4* ±27.4	61.3* ±25.6	65.3* ±25.4	50.8* ±11.8
Cotton cloth treated with acetone over 1 milliliter of sweat	138.9 ±26.7	71.4* ±30.6	71.1* ±24.3	67.8* ±26.0	61.7* ±25.9
Untreated cotton cloth over 1 gram per kilogram of body weight of pyrax powder	130.1 ±21.6	58.7* ±12.6	57.3* ±17.9	55.4* ±17.5	54.4* ±15.9

* Significantly different from pretest mean at 0.01 level of probability. Pathological review of liver failed to uncover developing abnormalities. Change was not attributed to test compound effect.

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TABLE 5. 24-DAY RABBIT WEAR TEST - SUMMARY OF BUN RESULTS (mg/dl)

Type Application	Pretest (7 Weeks) Mean±SD	Period of Test - Mean±SD Day 5	Day 12	Day 19	Day 24
Exposed					
Cotton cloth treated with resmethrin (0.247 mg/cm^2)	16.8 ±1.7	19.8* ±4.0	15.4 ±3.4	15.3 ±2.6	22.8* ±2.7
Cotton cloth treated with resmethrin (0.247 mg/cm^2) over 1 milliliter of sweat (ref Appendix D)	18.3 ±2.3	18.5 ±4.4	19.5 ±10.2	13.5* ±2.8	22.6* ±3.4
Cotton cloth treated with acetone over 10 grams of technical grade resmethrin	17.5 ±3.3	14.2 ±3.2	17.7 ±4.7	17.4 ±3.7	22.5 ±6.5
Untreated cotton cloth over 1 gram per kilogram of body weight of 1 percent resmethrin in pyrax powder	17.3 ±2.9	14.5 ±2.1	15.4 ±3.3	18.4 ±1.8	21.4 ±5.2
Controls					
Cotton cloth treated with acetone	19.7 ±2.7	15.8* ±1.3	15.4* ±1.3	16.4 ±2.9	14.4* ±3.6
Cotton cloth treated with acetone over 1 milliliter of sweat	17.9 ±2.3	14.4 ±3.6	15.0 ±2.5	16.4 ±2.4	17.1 ±2.5
Untreated cotton cloth over 1 gram per kilogram of body weight of pyrax powder	16.5 ±2.1	13.4* ±2.4	16.0 ±2.5	17.0 ±3.1	22.8 ±5.4

* Significantly different from pretest mean at 0.01 level of probability. Pathological review of kidney failed to uncover developing abnormalities. Change was not attributed to test compound effect.

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APPENDIX J

TABLE 1. 14-DAY FEEDING STUDY - SUMMARY OF DIET CONSUMPTION AND DOSAGE DATA - FEMALE RATS (SPRAGUE-DAWLEY)

	Projected Dosage Resmethrin Levels (mg/kg/day)					
	Solvent Control	375	750	1500	3000	6000
Grams diet consumed/rat/day	13.5	13.9	12.9	12.5	12.5	3.2
Grams diet consumed/kg/day	90	86	84	82	89	28
Mean weight gain of rats during study (grams)	34	30	21	9	4	-38*
Feed utilization (total body weight gain/total food consumed)	0.17	0.14	0.11	0.05	0.02	-2.41
Grams water intake/rat/day	27.6	31.5	24.8	31.1	26.4	19.0
Grams water intake/kg/day	184	195	162	205	189	166
Mean terminal body weight (grams)	167	177	163	155	142	96
Actual mean dosage resmethrin (mg/kg/day)	---	323	630	1230	2670	1680

* Represents body weight decrease.

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TABLE 2. 14-DAY FEEDING STUDY - SUMMARY OF DIET CONSUMPTION AND DOSAGE DATA - MALE RATS (SPRAGUE-DAWLEY)

	Projected Dosage Resmethrin Levels (mg/kg/day)					
	Solvent Control	375	750	1500	3000	6000
Grams diet consumed/rat/day	19.5	18.6	18.4	16.8	11.0	14.2
Grams diet consumed/kg/day	85	83	88	83	64	85
Mean weight gain of rats during study (grams)	84	77	61	31	-20*	-51*
Feed utilization (total body weight gain/total food consumed)	0.29	0.28	0.22	0.12	-0.18	-0.65
Grams water intake/rat/day	31.5	35.2	33.7	36.2	28.1	24.8
Grams water intake/kg/day	138	158	162	180	164	149
Mean terminal body weight (grams)	270	261	239	216	161	135
Actual mean dosage resmethrin (mg/kg/day)	---	310	660	1250	1923	5100

* Represents body weight decrease.

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APPENDIX K

TABLE 1. 14-DAY FEEDING STUDY - SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS - FEMALE RATS (SPRAGUE-DAWLEY)

Dosage	Terminal Body Weight (gm)	Mean Organ-to-Body Weight Ratios (gms/100 gms body weight) ±SD			
		Lung	Liver	Kidney	Spleen
Solvent Control	167 ±9	0.70 ±0.09	4.07 ±0.17	0.82 ±0.06	0.31 ±0.02
375.0 mg/kg/day	177 ±7	0.71 ±0.04	4.65* ±0.02	0.81 ±0.06	0.28 ±0.03
750.0 mg/kg/day	163 ±8	0.69 ±0.06	5.37* ±0.22	0.90 ±0.05	0.28 ±0.04
1500.0 mg/kg/day	155 ±15	0.77 ±0.16	6.25* ±0.35	0.90 ±0.08	0.30 ±0.04
3000.0 mg/kg/day	142* ±12	0.74 ±0.07	7.22* ±0.39	0.94 ±0.10	0.29 ±0.08
6000.0 mg/kg/day	96* ±8	---	---	---	---

* Significantly different from solvent control at .01 level of probability.

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TABLE 2. 14-DAY FEEDING STUDY - SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS - MALE RATS (SPRAGUE-DAWLEY)

Dosage	Terminal Body Weight (gm)	Mean Organ-to-Body Weight Ratios (gms/100 gms body weight) ±SD				
		Lung	Liver	Kidney	Spleen	Testes
Solvent Control	270 ±17	0.54 ±0.05	4.79 ±0.33	0.82 ±0.08	0.25 ±0.02	1.06 ±0.06
375.0 mg/kg/day	261 ±17	0.58 ±0.06	5.30 ±0.29	0.85 ±0.11	0.25 ±0.03	1.00 ±0.08
750.0 mg/kg/day	239 ±18	0.62 ±0.16	5.58* ±0.27	0.94 ±0.08	0.27 ±0.04	1.17 ±0.14
1500.0 mg/kg/day	216* ±11	0.56 ±0.04	6.24* ±0.34	0.96 ±0.05	0.29 ±0.03	1.35* ±0.13
3000.0 mg/kg/day	161* ±8	0.70* ±0.02	7.77* ±0.63	1.04* ±0.05	0.26 ±0.03	1.40* ±0.15
6000.0 mg/kg/day	135* ±20	1.26* ---	6.80* ---	1.36* ---	--- ---	1.26 ---

* Significantly different from solvent control at 0.01 level of probability.

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APPENDIX L

TABLE 1. 14-DAY FEEDING STUDY - SUMMARY OF DIET CONSUMPTION AND DOSAGE DATA - FEMALE RATS (LONG-EVANS)

	Project Dosage Resmethrin Levels (mg/kg/day)						
	Solvent Control	94	188	375	750	1500	3000
Grams diet consumed/rat/day	15.6	15.9	15.5	16.5	13.5	9.8	10.5
Grams diet consumed/kg/day	93.6	97.4	95.8	103.0	89.0	72.5	84.4
Mean weight gain of rats during study (grams)	50.2	45.6	44.0	41.6	32.8	-4.8*	-19.3*
Feed utilization (total body weight gain/total food consumed)	0.21	0.19	0.19	0.17	0.16	-0.03	-0.87
Grams water intake/rat/day	32.9	26.8	26.4	25.4	23.7	19.8	39.7
Grams water intake/kg/day	197.6	164.0	163.7	159.0	156.0	147.0	318.0
Mean terminal body weight (grams)	192.1	186.5	184.5	181.3	168.3	137.3	116.1
Actual mean dosage resmethrin (mg/kg/day)	--	90	180	386	668	1080	2532

* Represents body weight loss.

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TABLE 2. 14-DAY FEEDING STUDY - SUMMARY OF DIET CONSUMPTION AND DOSAGE DATA - MALE RATS (LONG-EVANS)

	Projected Dosage Resmethrin Levels (mg/kg/day)						
	Solvent Control	94	188	375	750	1500	3000
Grams diet consumed/rat/day	16.3	12.4	15.2	15.4	14.6	14.6	6.3
Grams diet consumed/kg/day	83.8	64.8	78.7	79.3	77.9	91.7	42.2
Mean weight gain of rats during study (grams)	48.1	42.8	35.6	39.6	26.1	-25.7*	-15.2*
Feed utilization (total body weight gain/total food consumed)	0.18	0.20	0.15	0.16	0.11	-0.15	-0.68
Grams water intake/rat/day	33.7	19.6	23.8	26.0	29.5	32.1	20.3
Grams water intake/kg/day	172.8	102.3	123.4	133.7	156.9	200.7	135.8
Mean terminal body weight (grams)	219.3	218	211.5	215.1	203.0	155.0	144.0
Actual mean dosage resmethrin (mg/kg/day)	---	60.9	147.9	297.3	584.0	1375.0	1266.0

* Represents body weight loss.

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APPENDIX M

TABLE 1. 14-DAY FEEDING STUDY - SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS - FEMALE RATS (LONG-EVANS)

Dosage	Terminal Body Weight (gm)	Mean Organ-to-Body Weight Ratios (gms/100 gms body weight)±SD Lung	Liver	Kidney	Spleen
Solvent Control	192.0 ±18.2	0.62 ±0.08	5.53 ±0.68	0.91 ±0.15	0.28 ±0.04
94 mg/kg/day	186.5 ±12.4	0.71 ±0.07	4.87 ±0.62	0.84 ±0.15	0.28 ±0.03
188 mg/kg/day	184.5 ±11.0	0.84 ±0.17	5.02 ±0.88	0.87 ±0.14	0.27 ±0.04
375 mg/kg/day	181.3 ±8.3	0.91 ±0.28	6.60 ±0.44	0.87 ±0.06	0.27 ±0.04
750 mg/kg/day	168.3 ±13.9	0.98 ±0.43	6.95* ±0.68	0.92 ±0.05	0.27 ±0.03
1500 mg/kg/day	137.3* ±15.6	1.10 ±0.36	9.94* ±1.38	0.98 ±0.17	0.25 ±0.03
3000 mg/kg/day	---	---	---	---	---

* Significantly different from solvent control at 0.01 level of probability

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TABLE 2. 14-DAY FEEDING STUDY - SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS - MALE RATS (LONG-EVANS)

Dosage	Terminal Body Weight (gm)	Mean Organ-to-Body Weight Ratios (gms/100 gms body weight)±SD Lung	Liver	Kidney	Spleen	Testes
Solvent Control	219.3 ±33.7	1.18 ±0.50	4.78 ±0.20	0.88 ±0.12	0.24 ±0.03	1.22 ±0.21
94 mg/kg/day	218.0 ±34.1	0.69 ±0.27	4.68 ±0.45	0.90 ±0.12	0.24 ±0.05	1.15 ±0.20
188 mg/kg/day	211.5 ±31.8	0.70 ±0.15	4.99 ±0.62	0.91 ±0.06	0.24 ±0.03	1.24 ±0.18
375 mg/kg/day	215.2 ±22.8	0.87 ±0.40	6.10* 0.32	0.97 0.08	0.21 0.04	1.17 0.07
750 mg/kg/day	203.0 ±17.8	0.81 ±0.22	6.91* ±1.06	0.93 ±0.11	0.20 ±0.02	1.25 ±0.15
1500 mg/kg/day	155.0* ±25.2	0.91 ±0.46	8.29* ±0.86	0.99 ±0.08	0.22 ±0.03	1.45 ±0.26
3000 mg/kg/day	---	---	---	---	---	---

* Significantly different from solvent control at 0.01 level of probability. Pathological review of liver failed to uncover developing abnormalities. Change was not attributed to test compound effect.

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APPENDIX N

90-DAY FEEDING STUDY
GENERAL DESCRIPTION OF TEST PLAN

A 90-day feeding study was conducted with Long-Evans rats. The males weighed 220-270 grams and the females weighed 160-190 grams when submitted to test and had been preconditioned to the special feeding study cages and ground feed for 2 weeks prior to the start of the study. The level of resmethrin in the feed was established in accordance with the data obtained in a 14-day feeding study on Sprague-Dawley Wistar-derived rats. Dosages calculated at 0.5 $\log_{10}$ intervals were as follows:

Projected Dosages mg/kg/day	Actual Dosages mg/kg/day Male	Female
Acetone Solvent Control	0.0	0.0
3	--	2.7
8	--	7.0
25	21.7	22.2
75	66.3	66.5
240	210.8	219.2
750	678.5	723.8
2400	---	---*

* Rats died before accurate food consumption could be measured.

Concentrations of resmethrin in the feed were adjusted every 2 weeks in order to maintain a constant dosage level. All rats remaining at the end of the 13 week test period were sacrificed at which time blood samples were taken via cardiac puncture for clinical chemistry tests. Organ-body weight ratios were determined and selected tissue sections were saved for pathological examination.

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APPENDIX O

TABLE 1. 90-DAY FEEDING STUDY - SUMMARY OF DIET CONSUMPTION AND DOSAGE DATA - FEMALE RATS

	Projected Dosage Resmethrin Levels (mg/kg/day)							
	Solvent Control	3	8	25	75	240	750	2400
Grams diet consumed/ rat/day	16.2	15.5	16.0	15.7	15.5	14.7	13.5	---*
Grams diet consumed/ kg/day	64.5	61.1	62.4	65.0	60.5	61.7	66.6	---
Mean weight gain of rats during study (grams)	110.2	112.6	118.2	96.7	103.9	79.6	60.4	---
Feed utilization (total body weight gain/total food consumed)	.015	.016	.016	.013	.015	.012	.010	---
Grams water intake/ rat/day	37.2	38.5	38.3	36.3	33.8	33.2	33.5	---
Grams water intake/ kg/day	146.0	150.1	146.8	147.9	131.6	138.1	168.9	---
Mean terminal body weight (grams)	278.1	252.2	292.9	266.4	293.2	247.6	221.0	---
Actual mean dosage resmethrin (mg/kg/day)	---	2.7	7.0	22.2	66.5	219.2	723.8	

* Rats died before accurate food consumption could be measured.

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TABLE 2. 90-DAY FEEDING STUDY - SUMMARY OF DIET CONSUMPTION AND DOSAGE DATA - MALE RATS

	Projected Dosage Resmethrin Levels (mg/kg/day)				
	Solvent Control	25	75	240	750
Grams diet consumed/rat/day	20.1	21.1	20.9	21.1	19.2
Grams diet consumed/kg/day	54.2	56.9	57.9	58.4	64.0
Mean weight gain of rats during study (grams)	190.3	194.2	200.8	192.4	114.9
Feed utilization (total body weight gain/total food consumed)	.020	.020	.021	.020	.013
Grams water intake/rat/day	44.1	43.8	44.3	43.3	44.9
Grams water intake/kg/day	114.3	117.4	122.3	119.4	149.9
Mean terminal body weight (grams)	448.3	440.8	432.7	433.2	359.3
Actual mean dosage resmethrin (mg/kg/day)	---	21.7	66.3	210.8	678.5

APPENDIX P

TABLE 1. 90-DAY FEEDING STUDY - SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS - FEMALE RATS

Dosage	Terminal Body Weight (gm)	Mean Organ-to-Body Weight Ratios (gms/100 gms body weight) ±SD				
		Lung	Liver	Heart	Kidney	Spleen
Solvent Control	278 ±36	0.55 ±0.12	2.96 ±0.27	0.31 ±0.05	0.62 ±0.08	0.21 ±0.04
3 mg/kg/day	252 ±25	0.54 ±0.06	2.53* ±0.33	0.32 ±0.02	0.64 ±0.07	0.17 ±0.04
8 mg/kg/day	293 ±20	0.49 ±0.05	3.10 ±0.20	0.34 ±0.12	0.58 ±0.06	0.19 ±0.02
25 mg/kg/day	266 ±18	0.48 ±0.05	2.95 ±0.18	0.27 ±0.02	0.59 ±0.05	0.18 ±0.06
75 mg/kg/day	293 ±38	0.50 ±0.07	3.17 ±0.43	0.29 ±0.04	0.64 ±0.10	0.21 ±0.04
240 mg/kg/day	248 ±19	0.52 ±0.04	3.84* ±0.24	0.32 ±0.03	0.67 ±0.08	0.19 ±0.04
750 mg/kg/day	221* ±19	0.57 ±0.09	5.14* ±0.36	0.34 ±0.02	0.70 ±0.09	0.24 ±0.03
2400 mg/kg/day	---	---	---	---	---	---

* Significantly different from solvent control at 0.01 level of probability.

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TABLE 2. 90-DAY FEEDING STUDY - SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS - MALE RATS

Dosage	Terminal Body Weight (gm)	Mean Organ-to-Body Weight Ratios (gms/100 gms body weight) ±SD					
		Lung	Liver	Heart	Kidney	Spleen	Testes
Solvent Control	448 ±23	0.39 ±0.06	3.16 ±0.26	0.27 ±0.02	0.58 ±0.06	0.16 ±0.02	0.72 ±0.09
25 mg/kg/day	441 ±51	0.41 ±0.03	3.13 ±0.17	0.30 ±0.03	0.60 ±0.07	0.16 ±0.02	0.77 ±0.06
75 mg/kg/day	433 ±24	0.42 ±0.04	3.24 ±0.24	0.29 ±0.02	0.62 ±0.06	0.15 ±0.02	0.77 ±0.09
240 mg/kg/day	433 ±47	0.44 ±0.05	3.78* ±0.18	0.30 ±0.03	0.68* ±0.07	0.16 ±0.02	0.77 ±0.09
750 mg/kg/day	359* ±37	0.46 ±0.07	4.83* ±0.32	0.31* ±0.03	0.81* ±0.09	0.16 ±0.03	0.90* ±0.09

* Significantly different from solvent control at 0.01 level of probability.

APPENDIX Q

TABLE 1. 90-DAY FEEDING STUDY - SUMMARY OF CLINICAL CHEMISTRY RESULTS - FEMALE RATS

Clinical Chemistry Test	Dosage Group (mg/kg/day) Solvent n(20)	3 n(9)	8 n(10)	25 n(10)	75 n(10)	240 n(10)	750 n(10)
			Mean±SD				
SGOT (International Units/Liter)	286.8 ±141.6	303.1 ±127.1	246.0 ±73.0	183.4 ±55.1	227.5 ±143.1	235.6 ±136.0	216.0 ±53.6
SGPT (International Units/Liter)	76.3 ±36.6	68.7 ±32.5	69.4 ±12.4	73.6 ±17.5	97.9 ±76.5	102.1 ±82.9	95.5 ±28.2
Total LDH (International Units/Liter)	1569.2 ±394.7	1755.6 ±292.2	1446.1 ±426.5	1143.7 ±322.6	1197.7 ±497.1	1042.1 ±355.2	1088.1 ±276.6
Alkaline Phosphatase (International Units/Liter)	214.6 ±78.3	95.6[a] ±37.1	187.8[a] ±37.5	225.6 ±84.5	245.6 ±45.7	241.9 ±86.2	388.3[a] ±85.9
GGTP (International Units/Liter)	0.80 ±1.00	0.33 ±0.71	0.50 ±0.97	1.30 ±0.82	3.10[a] ±1.90	0.30 ±0.48	3.60[b] ±3.70
Total Bilirubin (mg/dl)	0.52 ±0.22	0.53 ±0.13	0.42 ±0.08	0.34 ±0.05	0.41 ±0.09	0.40 ±0.06	0.44 ±0.13
Total Protein (mg/dl)	8.4 ±0.9	8.6 ±0.4	7.9 ±0.7	8.8 ±0.7	8.2 ±0.9	7.7 ±0.5	8.0 ±0.5
BUN (mg/dl)	27.4 ±4.5	21.4[b] ±2.3	22.3 ±1.5	26.3 ±3.4	26.9 ±4.9	27.0 ±5.2	29.0 ±5.1

n - number of rats per group.
a - significantly different from solvent control at <0.001 level of probability.
b - significantly different from solvent control at <0.005 level of probability.

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TABLE 2. 90-DAY FEEDING STUDY - SUMMARY OF CLINICAL CHEMISTRY RESULTS - MALE RATS

Clinical Chemistry Test	Solvent Control n(10)	Dosage Group (mg/kg/day) 25 n(10)	75 n(10)	240 n(10)	750 n(8)
		Mean±SD			
SGOT (International Units/Liter)	296.1 ±168.4	218.5 ±114.0	278.4 ±79.7	328.2 ±144.6	287.2 ±146.9
SGPT (International Units/Liter)	84.3 ±44.6	68.1 ±10.1	111.5 ±58.0	144.5 ±80.5	189.8 ±155.1
Total LDH (International Units/Liter)	1719.0 ±497.5	1251.9 ±375.2	1248.7 ±301.8	1582.3 ±320.1	1442.3 ±475.1
Alkaline Phosphatase (International Units/Liter)	279.8 ±29.9	247.7 ±58.9	355.5 ±85.2	279.0 ±79.3	399.8[a] ±88.7
GGTP (International Units/Liter)	1.9 ±4.1	1.3 ±1.2	1.6 ±2.0	0.3 ±0.9	2.0 ±2.3
Total Bilirubin (mg/dl)	0.49 ±0.11	0.42 ±0.08	0.46 ±0.11	0.40 ±0.16	0.29[a] ±0.08
Total Protein (mg/dl)	8.5 ±0.6	7.7[b] ±0.4	8.0 ±0.5	7.6[b] ±0.5	8.0 ±0.8
BUN (mg/dl)	19.5 ±2.7	22.4 ±2.1	21.6 ±4.2	20.9 ±2.9	24.1[c] ±3.9

n - number of rats per group.
[a] - significantly different from solvent control at <.002 level of probability.
[b] - significantly different from solvent control at <.005 level of probability.
[c] - significantly different from solvent control at <.01 level of probability.

APPENDIX R
21-DAY INTRAVENOUS STUDY
SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS
MALE DOGS

Dosage	Terminal Body Weight (kg)	Mean Organ-To-Body Weight Ratios (gms/100 gms body weight)±SD Lung	Liver	Kidney	Spleen	Testes
Solvent Control	11.96 ±1.44	1.22 ±0.24	3.70 ±0.25	0.67 ±0.05	0.96 ±0.17	0.17 ±0.04
10 mg/kg	12.03 ±1.64	1.31 ±0.04	3.98 ±0.37	0.77 ±0.09	0.79 ±0.16	0.19 ±0.01
25 mg/kg	12.80 ±3.25	1.52 ±0.29	3.82 ±0.79	0.76 ±0.09	0.83 ±0.19	0.16 ±0.01

APPENDIX S

TABLE 1. 21-DAY INTRAVENOUS STUDY - SUMMARY OF CLINICAL CHEMISTRY RESULTS - MALE DOGS

Clinical Chemistry Test	Dosage Group	Pretest 6-Week Mean±SD	Period of Test (Mean±SD) Day 1	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21
SGOT (International Units/Liter)	Solvent Control	32 ±7	30 ±9	23 ±2	26 ±4	22 ±3	26 ±5	23 ±4	22 ±4
	10 mg/kg	32 ±10	30 ±12	22 ±5	26 ±6	19 ±3	26 ±10	27 ±6	26 ±11
	25 mg/kg	33 ±6	26 ±1	17* ±1	22 ±4	20 ±2	25 ±1	21 ±3	21 ±6
SGPT (International Units/Liter)	Solvent Control	41 ±9	86 ±60	72 ±33	44 ±11	34 ±8	52 ±13	36 ±6	35 ±4
	10 mg/kg	41 ±12	239* ±335	164* ±193	60 ±45	46 ±36	38 ±21	56 ±29	63 ±45
	25 mg/kg	43 ±9	95 ±29	90 ±47	34 ±11	29 ±5	45 ±24	34 ±14	24 ±3
LDH (International Units/Liter)	Solvent Control	44 ±17	43 ±6	55 ±30	39 ±5	46 ±18	64 ±21	66 ±37	64 ±21
	10 mg/kg	43 ±19	31 ±26	56 ±23	53 ±5	96* ±12	184* ±92	118* ±8	69 ±14
	25 mg/kg	42 ±17	42 ±10	47 ±8	53 ±25	93* ±40	132* ±70	100* ±21	68 ±0

* Significantly different from solvent control at the .01 level of probability.

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TABLE 2. 21-DAY INTRAVENOUS STUDY - SUMMARY OF CLINICAL CHEMISTRY RESULTS - MALE DOGS

Clinical Chemistry Test	Dosage Group	Pretest 6-Week Mean±SD	Period of Test (Mean±SD) Day 1	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21
Alkaline Phosphatase (International Units/Liter)	Solvent Control	59 ±19	69 ±28	66 ±20	95 ±69	74 ±35	71 ±24	73 ±20	84 ±20
	10 mg/kg	39 ±8	60 ±30	59 ±25	52 ±15	57 ±29	68 ±22	59 ±1	49 ±7
	25 mg/kg	52 ±16	67 ±19	97 ±3	78 ±14	89 ±29	134 ±115	98 ±59	72 ±8
Bilirubin (mg/dl)	Solvent Control	0.3 ±0.1	0.5 ±0.3	0.4 ±0.2	0.4 ±0.2	0.3 ±0.0	0.3 ±0.1	0.3 ±0.1	0.3 ±0.1
	10 mg/kg	0.3 ±0.1	0.4 ±0.1	0.3 ±0.1	0.3 ±0.1	0.4 ±0.1	0.2 ±0.1	0.2 ±0.0	0.4 ±0.1
	25 mg/kg	0.3 ±0.1	0.3 ±0.1	0.3 ±0.1	0.3 ±0.1	0.4 ±0.2	0.3 ±0.2	0.3 ±0.1	0.5 ±0.1
GGTP (International Units/Liter)	Solvent Control	6 ±3	8 ±5	5 ±3	6 ±2	4 ±2	6 ±1	9 ±5	3 ±1
	10 mg/kg	6 ±2	7 ±3	5 ±2	7 ±0	3 ±3	5 ±1	10 ±8	4 ±1
	25 mg/kg	6 ±3	7 ±2	5 ±1	6 ±2	4 ±2	6 ±1	12 ±6	4 ±1

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TABLE 3. 21-DAY INTRAVENOUS STUDY -SUMMARY OF CLINICAL CHEMISTRY RESULTS - MALE DOGS

Clinical Chemistry Test	Dosage Group	Pretest 6-Week Mean±SD	Period of Test (Mean±SD) Day 1	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21
BUN (mg/dl) Urea Nitrogen)	Solvent Control	21.0 ±6.5	21.0 ±6.1	14.9 ±6.8	18.4 ±9.3	19.7 ±6.9	18.4 ±8.7	16.0 ±4.6	18.1 ±8.2
	10 mg/kg	19.4 ±5.6	15.1 ±2.0	12.3 ±2.3	15.7 ±1.7	13.3 ±2.4	11.4 ±2.8	13.2 ±3.5	16.2 ±5.4
	25 mg/kg	17.6 ±3.0	13.0 ±3.5	7.7 ±2.5	13.1 ±4.4	13.6 ±6.1	13.3 ±4.9	13.0 ±2.9	14.5 ±1.4
Sodium (mEq/L)	Solvent Control	146 ±2	---	147 ±2	148 ±4	150 ±1	151 ±1	147 ±1	148 ±0
	10 mg/kg	145 ±1	---	147 ±2	149 ±2	150 ±2	151 ±2	149 ±1	147 ±3
	25 mg/kg	147 ±1	---	147 ±1	148 ±2	151 ±4	152 ±2	148 ±1	150 ±1
Potassium (mEq/L)	Solvent Control	4.2 ±0.3	---	4.0 ±0.5	4.1 ±0.3	4.3 ±0.3	4.3 ±0.5	4.2 ±0.3	4.3 ±0.4
	10 mg/kg	4.5 ±0.2	---	4.4 ±0.2	4.2 ±0.3	4.3 ±0.2	4.4 ±0.1	4.7 ±0.3	4.7 ±0.3
	25 mg/kg	4.5 ±0.2	---	4.3 ±0.2	4.2 ±0.3	4.2 ±0.2	4.4 ±0.4	4.5 ±0.1	4.6 ±0.1

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TABLE 4. 21-DAY INTRAVENOUS STUDY - SUMMARY OF CLINICAL CHEMISTRY RESULTS - MALE DOGS

Clinical Chemistry Test	Dosage Group	Pretest 6-Week Mean±SD	Period of Test (Mean±SD) Day 1	Day 3	Day 7	Day 10	Day 14	Day 17	Day 21
RBC Cholinesterase (Garry and Routh Units)	Solvent Control	12.1 ±4.8	10.5 ±3.7	10.3 ±4.5	10.5 ±4.7	10.7 ±4.7	11.2 ±5.5	11.4 ±5.1	8.2 ±4.9
	10 mg/kg	13.5 ±3.2	12.5 ±4.1	11.6 ±3.5	11.5 ±3.9	12.8 ±4.4	11.7 ±3.9	11.4 ±4.0	10.7 ±3.8
	25 mg/kg	13.6 ±2.4	13.6 ±1.6	12.8 ±0.0	12.3 ±0.6	13.1 ±2.0	12.8 ±0.8	12.7 ±1.7	11.9 ±3.2
Plasma Cholinesterase (Garry and Routh Units)	Solvent Control	15.3 ±2.5	15.4 ±2.4	14.6 ±2.0	16.6 ±1.5	17.1 ±1.8	17.2 ±2.2	17.4 ±1.9	17.7 ±2.0
	10 mg/kg	16.3 ±2.1	16.1 ±1.5	16.1 ±2.0	16.3 ±0.3	17.0 ±0.7	15.6 ±1.6	16.4 ±1.3	17.0 ±1.5
	25 mg/kg	15.0 ±2.4	15.6 ±1.8	15.1 ±2.0	13.5 ±1.8	14.1 ±1.9	14.2 ±2.6	14.2 ±1.6	14.6 ±1.1